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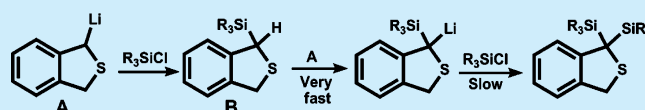
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Preferential Geminal Bis-silylation of 3,4-Benzothiophane Is Caused by the Dominance of Electron Withdrawal by R_3Si over Steric Shielding EffectsYifeng Han,[†] Yun Ma,[‡] Ivan Keresztes,[‡] David B. Collum,^{*,‡} and E. J. Corey^{*,†}[†]Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States[‡]Department of Chemistry and Chemical Biology Baker Laboratory, Cornell University, Ithaca, New York 14853-1301, United States

S Supporting Information

ABSTRACT: Benzylic C–H lithiation of 3,4-benzothiophane and subsequent treatment with triphenyl- or trimethylchlorosilane under a variety of conditions leads to α,α' - rather than α,α' -bis-silylation products as a consequence of anion stabilization by R_3Si and very fast deprotonation of the intermediate monosilylated product, even with a sterically bulky base such as lithium diisopropylamide.



The origin of the research reported herein was the question of whether chiral cyclic sulfides of general structure **1** (or enantiomers) might be useful for catalytic enantioselective methylene transfer to $C=C$ or $C=O$ from methylene precursors such as Et_2Zn/ICH_2Cl or Zn/CH_2I_2 , following a process in which **1** serves as a carrier to provide chiral ylide **2**.¹ Initial studies were directed toward the synthesis of α,α' -bis-silanes such as **1**, $R = Me_3Si$, Ph_3Si , and $t-BuMe_2Si$, from the readily available starting material **3** (Figure 1).² It seemed

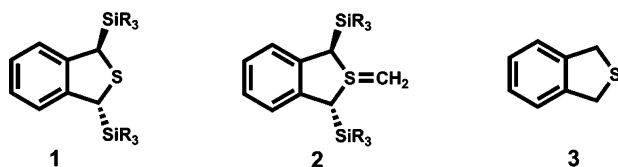
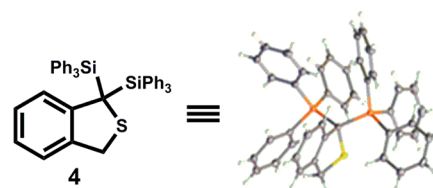


Figure 1. Some 3,4-benzothiophanes.

reasonable that rapid access to the series of silyl ligands **1** might be secured simply by sequential, one-flask silylation of monoanions derived from **3** or by one-step bis-silylation of the α,α' -dianion of **3**, a 12- π -electron (non-Hückel stabilized) system. Surprisingly, however, access to the desired 2,5-bis-silylated 3,4-benzothiophane structure proved to be difficult because the behavior of anions desired from **3** was strongly influenced by the electronic and steric effects of silyl substituents.

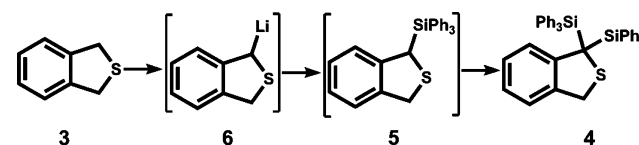
Reaction of **3** in THF at $-78\text{ }^\circ\text{C}$ ³ with 1.0 equiv of $n\text{-BuLi}$ (2.5 M in hexanes) for 3 h followed by slow addition of Ph_3SiCl (in THF at $-78\text{ }^\circ\text{C}$) afforded as major product (along with unreacted **3**) the crystalline gem-bis-silane **4** in 31% yield.³ The structure of **4** was established by X-ray crystallographic analysis (Figure 2).⁴

The formation of **4** likely occurs via the C(2)-monosilylation product **5** by further deprotonation at C(2) (either by monolithiated **3** or residual $BuLi$) followed by a second

Figure 2. X-ray crystallographic structure of **4**.

silylation (Scheme 1). The putative intermediate **5** could be obtained by the gradual addition of a cold ($-78\text{ }^\circ\text{C}$) solution of

Scheme 1. Facile Geminal Silylation



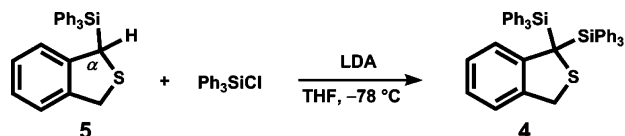
lithium diisopropyl amide (LDA) in THF to a mixture of **3** and 1.0 equiv of Ph_3SiCl in THF at $-78\text{ }^\circ\text{C}$, which gave **5** in 42% yield along with recovered **3** (40%).

Consistent with these observations was the finding that the addition of 1.0 equiv of LDA in THF (at $-78\text{ }^\circ\text{C}$) to a solution of **5** and Ph_3SiCl in THF at $-78\text{ }^\circ\text{C}$ afforded **4** (76%) as major product, without the formation of a detectable amount of the α,α' -silylated product **1**, $R = Ph$ (Scheme 2). Evidently even with the use of the very bulky base LDA, the acidifying effect of an C(2) Ph_3Si group is sufficiently great to override its steric shielding of the geminal C(2)-H proton. An α -triphenylsilyl group has been found to increase the acidity of the C(9)-proton of fluorene by about 10^4 in previous work.^{5,6} Despite

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Scheme 2. Preferential Geminal Triphenylsilylation



extensive experimentation, no conditions could be found to convert **3** to the α,α' -bis-silylated derivative **1**, R = Ph.

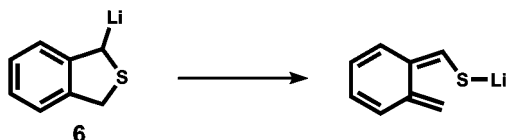
The same preference for the formation of *gem*-bis-silylated product was demonstrated using Me₃SiCl as the silylation reagent. Thus, the addition of **3** to a mixture of 2.0 equiv of LDA and 6.0 equiv of TMSCl at $-78\text{ }^{\circ}\text{C}$ produced the *gem*-bis-silylation product **7** in 64% yield with no measurable amount of the isomeric α,α' -bis-TMS compound (Figure 3).



Figure 3. Possible position isomers for disilylation.

At this point, it should be mentioned that all of the above silylation reactions must be carried out at low temperatures because the intermediate **6** is unstable above $-60\text{ }^{\circ}\text{C}$. There is considerable precedent for decomposition via the cyclo-elimination pathway shown in Scheme 3.⁷

Scheme 3. Possible Pathway for Anion Decomposition



¹H, ⁶Li, and ¹³C NMR studies were carried out at $-78\text{ }^{\circ}\text{C}$ to ascertain the nature of the lithiated intermediate (**6**) generated from **3** under various lithium–hydrogen exchange conditions. Reaction of **3** with *n*-butyllithium in THF at $-78\text{ }^{\circ}\text{C}$ occurred with a half-life ($t_{1/2}$) of greater than 1 h and gave only the monolithiated form, **6** (Scheme 1).⁴ The ¹H, ⁶Li, and ¹³C NMR spectra on samples generated using [⁶Li] *n*-BuLi showed asymmetry attesting to monolithiation, and the appearance of the benzylic CH₂ moiety as an A–B quartet showed that the ⁶Li counterion differentiated the two faces. Although we observed no evidence to indicate aggregation, it cannot be rigorously excluded either. No other lithiated species could be observed even using more than 2 equiv of *n*-BuLi at $-78\text{ }^{\circ}\text{C}$ for 12 h, and quenching after 12 h with MeOD led to only monodeuterated **3**.⁴

Although the reaction of monolithium intermediate **6** with triphenylchlorosilane occurs readily at $-78\text{ }^{\circ}\text{C}$ to form **5**, NMR studies showed that proton transfer from **5** to **6** is even faster to form the silyl stabilized lithio-anion **9**. Further, NMR measurements also revealed that the reaction of **9** with Ph₃SiCl (Scheme 4) is slower than expected and requires several hours at $-78\text{ }^{\circ}\text{C}$. The slower rate of the silylation **9** to **4** appears to be a consequence of the anion-stabilizing effect (electron withdrawal) of Ph₃Si combined with the steric shielding by Ph₃Si in both **9** and Ph₃SiCl.

Scheme 4. NMR Rate Studies



The research described above has revealed significant nuances in the behavior of lithiation products derived from 3,4-benzothiane involving surprising rates of C–H lithiation and C–Li silylation.

■ ASSOCIATED CONTENT

S Supporting Information

Experimental procedures and characterization data for all reactions and products, including copies of ¹H NMR and ¹³C NMR spectra and single-crystal X-ray diffraction analysis. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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